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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,199	12/20/2001	Norbert Maurer	INEX.P-005	6234

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EXAMINER

KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
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1615

DATE MAILED: 06/27/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
10/019,199

Applicant(s)
Maurer

Examiner
Gollamudi Kishore

Art Unit
1615



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 13-32 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9 6) ☐ Other:

Art Unit: :1615

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 13-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hope (6,447,800) in view of Wheeler (5,976,567) or WO 98/51278 of record.

Hope discloses a method of preparation of liposomes containing a variety of active agents. The method involves combining already formed liposomes with an active agent and organic solvent, ethanol (at least 10 %), allowing a certain amount of time and diluting the organic solvent in the external phase. The presence of organic solvent according to Hope increases the permeability of the membrane (without disrupting the liposomes) and when the organic solvent is diluted, the permeability decreases (note col. 7, lines 32-65; Examples and claims). What is lacking in Hope is the use of a cationic lipid and the teachings of the removal of the organic solvent.

Wheeler while disclosing liposomal formulations containing nucleic acids using ethanol in the method teaches that cationic lipids such as DOTAP and DOTMA are efficient carriers of negatively charged nucleic acids for transfection (note the abstract and

Art Unit: :1615

col. 1, line 55 et seq.; Examples and claims. Wheeler's compositions further include PEG derivatized phospholipids (col. 11, lines 28-32). Although Wheeler's method does not involve using preformed liposomes, it is interesting to note Wheeler's teachings on col. 2, line 16 et seq., that loading of nucleic acids into preformed liposomes is practiced in the art. Wheeler's method involves similar procedure to the claimed method, except that the preformed liposomes are not used and the method of preparation involves the removal of ethanol by art known methods such as rotary evaporation (col. 18, line 40 through col. 19, line 12).

WO 98 while teaching compositions containing DOPAP, DSPC, cholesterol teaches that PEG derivatized lipids provide steric stabilization and prevent the aggregation of the particles; WO therefore, includes PEG-lipids such as PEG-ceramides. The buffer used in the preparations is a citrate buffer (note the abstract, pages 17-19 and claims).

The use of cationic lipids in the method of Hope, if the active agent involves a nucleic acid would have been obvious to one of ordinary skill in the art since Wheeler teaches that cationic lipids are efficient in transfecting cells with nucleic acids in a similar method of preparation involving ethanol. The removal of the already diluted ethanol in the external medium of Hope if it is deemed undesirable would have been obvious to one of ordinary skill in the art since Wheeler shows that the external ethanol can be removed by art known methods. The criticality of citrate buffer is not readily apparent to the examiner since the selection of the buffer depends upon the desired pH.

Art Unit: :1615

The inclusion of PEG-lipids in the compositions of Hope would have been obvious to one of ordinary skill in the art since WO teaches their ability to provide steric stabilization. The use of citrate buffer would have been obvious to one of ordinary skill in the art since WO teaches it is a commonly used buffer in liposomal compositions.

4. Claims 13-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hope (6,447,800) in view of Malone (PNAS, vol. 86, pp. 6077-6081, 1989) and Zalipsky (6,365,179).

As discussed above, Hope discloses a method of preparation of liposomes containing a variety of active agents. The method involves combining already formed liposomes with an active agent and organic solvent, ethanol (at least 10 %), allowing a certain amount of time and diluting the organic solvent in the external phase. The presence of organic solvent according to Hope increases the permeability of the membrane (without disrupting the liposomes) and when the organic solvent is diluted, the permeability decreases (note col. 7, lines 32-65; Examples and claims). What is lacking in Hope is the use of a cationic lipid and the teachings of the removal of the organic solvent. what is also lacking in Hope is the use of a modified lipid such as PEG-phospholipid.

Malone teaches that the use of cationic liposomes containing DOTMA is an efficient way of RNA transfection (note the abstract and discussion).

Art Unit: :1615

Zalipsky while disclosing liposomal formulations, teaches that modified lipids such as polymer derivatized lipids (PEG-phospholipids) extend the blood circulation time of the liposomes (col. 10, lines 28-37; col. 11, lines 12-57). The method of preparation in Zalipsky involves the use of ethanol and Zalipsky advocates the removal of ethanol by diafiltration (note Example 4 on col. 17).

The use of cationic lipid, DOTMA in the method of Hope, if the active agent involves a nucleic acid would have been obvious to one of ordinary skill in the art since Malone teaches that this cationic lipid is efficient in transfecting cells with nucleic acids. The removal of the already diluted ethanol in the external medium of Hope if it is deemed undesirable would have been obvious to one of ordinary skill in the art since Zalipski teaches that the external ethanol can be removed by diafiltration. The use of modified lipids in Hope would have been obvious to one of ordinary skill in the art since Zalipski also teaches that these lipids extend the circulation time of the liposomes. The criticality of citrate buffer is not readily apparent to the examiner since the selection of the buffer depends upon the desired pH.

4. Claims 13-20, and 25-32 are rejected under 35 U.S.C. 103(a) as being unpatentable Schubert (Chemistry and Physics of Lipids, 58, 121-129, 1991) in view of Malone (PNAS, vol. 86, pp. 6077-6081, 1989) and either Zalipsky (6,365,179) or WO 98/51278 of record.

Schubert discloses a method of loading preformed liposomes by detergent-induced (destabilizing agent-induced) formation of transient membrane holes. The method involves

Art Unit: :1615

the incubation of the preformed liposomes with the active agent such as nucleic acids and removal of the detergent (note the abstract and Materials and Method section). What is lacking in Schubert is the use of a cationic lipid. what is also lacking in Schubert is the use of a modified lipid such as PEG-phospholipid or PEG-ceramide.

Malone teaches that the use of cationic liposomes containing DOTMA is an efficient way of RNA transfection (note the abstract and discussion).

Zalipsky while disclosing liposomal formulations, teaches that modified lipids such as polymer derivatized lipids (PEG-phospholipids) extend the blood circulation time of the liposomes (col. 10, lines 28-37; col. 11, lines 12-57).

As discussed above, WO 98 while teaching compositions containing DOPAP, DSPC, cholesterol teaches that PEG derivatized lipids provide steric stabilization and prevent the aggregation of the particles; WO therefore, includes PEG-lipids such as PEG-ceramides. The buffer used in the preparations is a citrate buffer (note the abstract, pages 17-19 and claims).

The use of cationic lipid, DOTMA in the method of Schubert would have been obvious to one of ordinary skill in the art since Malone teaches that this cationic lipid is efficient in transfecting cells with nucleic acids. The use of modified lipids in Schubert would have been obvious to one of ordinary skill in the art since Zalipski also teaches that these lipids extend the circulation time of the liposomes or since WO 98 teaches their ability to sterically stabilize the particles. The criticality of citrate buffer is not readily apparent to

Art Unit: :1615

the examiner since the selection of the buffer depends upon the desired pH; one of ordinary skill in the art would be motivated to use citrate buffer since WO teaches that it is commonly used in liposomal preparations containing nucleic acids.

The reference of Lenk (5,262,168) which teaches the removal of ethanol by rotoevaporation and the use of citrate buffers in liposomal formulations is cited of interest (note col. 2, lines 44-45 and Example 1).

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

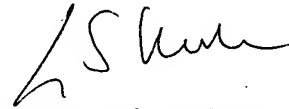
Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility

Art Unit: :1615

that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.



Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

June 25, 2003